Atty. Docket No.: 18747/2012 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Craig et al.	Examiner:	Peter Paras, Jr.
Serial No.:	10/068,460		
Filed:	February 6, 2002	Group Art Unit:	1632
Titled:	Insect Control System		
		Conf. No.:	8894

DECLARATION UNDER 37 CFR 1.132 BY

CHARALAMBOS SAVAKIS, M.D, PH.D AND ROGER CRAIG, PH.D

I declare:

1. I, Charalambos Savakis hold a M.D. degree from the University of Athens, Greece, and a Ph.D. degree in Cell and Developmental Biology from Harvard University. I received my M.D. degree in 1974 and my Ph.D. degree in 1981. My current position is Professor of Molecular Biology and Molecular Genetics, Faculty of Medicine, University of Crete, Greece. I have held this position since 1995. Previously, I held the position of Associate Professor of Molecular and Cell Biology at the same School, from 1987. Since 1984 I also hold the position of Adjunct Researcher, Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology Hellas (IMBB-FoRTH). I am co-inventor of the above-referenced patent application.

2. I, Roger K. Craig hold a Ph.D. degree in Biochemistry from the University of Aberdeen, Scotland UK. I received my Ph.D. degree in 1973. My current position is Chairman of Minos BioSystems Ltd and I have held this position since 2000. I am also currently an entrepreneur and independent consultant within the Biotechnology industry. Previous positions include Professor of Biochemistry at the Middlesex Hospital Medical School, London UK, and Head of Biotechnology at ICI Pharmaceuticals PLC. I have in the last ten years been actively involved as founder of a number of UK based Biotechnology start-up companies. I am co-inventor of the above-referenced patent application.

3. I have read the Office Action dated May 18, 2004, filed in the above-referenced patent application and understand that the Examiner has rejected claims 1-14 and 21, for alleged failing to comply with the enablement and written description requirements.

4. Our laboratory has developed a method for controlling a population of target insects. The method involves providing a gene encoding one constituent of a enzyme/pro-pesticide system linked to a sex-specific regulatory element; transforming target insects with the gene and allowing the gene to spread within the targeted insects. The insects are then given a second constituent of the enzyme/pro-pesticide system, which results in the conversion of the pro-pesticide to a pesticide.

5. As discussed in detail in the Amendment and Response, filed concurrently herewith, the teachings of the above referenced application, in view of what is known in the art, fully enables one of ordinary skill in the art to perform the method of controlling an insect population as recited in claims 1-14 and 21. Particularly, the instant application teaches that the transformed insects are released into wild-type populations to control the wild-type insect population. The instant application teaches this on page 13, line 27 through page 14, line 1, wherein it is stated:

> According to the present invention, insects are generated which can be released into wild-type populations of insects. The transgenic insects of the invention will consequently interbreed with the wild-type populations to produce target insects which are susceptible to a proinsecticide. The invention thus relates to an insect of a given sex, which insect has been transformed with a gene comprising a coding sequence encoding one constituent of an enzyme/pro-drug system and a promoter capable of driving the coding sequence substantially only in insects of the opposite sex. Preferably, the insect is a male insect. Preferably the insect can be mass reared.

The instant application also teaches on page 18, lines 28-30:

> A highly susceptible strain is bred and male flies isolated. Introduction of male flies into a population of non-transgenic flies results in rapid transfer of the transgene. Female flies which are born

> inheriting the transgene are susceptible to 5-FC, whilst male files remain resistant.

In view of the above, the instant application provides sufficient guidance to enable one of ordinary skill in the art to successfully control a wild-type insect population by the claimed method.

The attached publications demonstrate that in view of what is known in the art, and further in view of the instant application, the full scope of claims 1-14 and 21 are properly enabled.

Attached hereto is Exhibit A (Schliekelman and Gould, (2000) J. Econ. Entomology, 93(6); 1543-65) demonstrating the release of insects carrying a female killing or sterilization allele. The publication teaches the effectiveness of and optimal strategies for release of conditional lethal insects into a wild-type population. The publication examines the effect of varying the release size, number of generations until the conditional lethality, nonconditional fitness cost resulting from gene insertions, and fitness reduction associated with laboratory rearing on the efficiency of a conditional lethal release. The publication states at page 1548

> Sterile male and other genetic control releases have generally been very large. Typically, releases have been at a frequency of once per week or more (e.g., Davidson [1974]), with released-to-wild ratios of 100:1 not uncommon (e.g. Davidson [1974]). A conditional lethal release should require much smaller release sizes at less frequent intervals.

The publication also states at page 1560:

> A great deal of theoretical work has been done on population dynamics and sterile male release (see Ito et al. 1989 for a review), and most results should apply to conditional lethal releases.

6. The attached references (Exhibits B-F) demonstrate that in view of what is known in the art, and further in view of the instant application, one of skill would predict that the claimed methods would be successful if performed with any of the sex-specific regulatory elements recited in the specification and/or described in the art.

The specification teaches both Drosophila and Medfly yolk protein regulatory elements. The instant application states on page 11, lines 15-26:

> Systems based on a number of Drosophila yolk protein genes have been characterized, (Ronaldson and Bownes, 1995, Genet Res 66:9-17) and used to effect female specific heterologous gene expression (see, Heinrich and Scott, 2000, PNAS 97:8229- 8232; Thomas et al., 2000, Science 287:2474-2476). Yolk protein genes have also been characterized for the Medfly (Rina and Savakin, 1991, Genetics 127:769-780). The conserved nature of yolk protein genes indicates that regulatory elements driving heterologous genes in female insects can be isolated and characterized using standard genetic approach..... In the case where the target insects are Medfly (*C. capitata*), the VG1 and VG2 promoters may be used as disclosed in Rina and Savakis, Genetics 127:769-80, 1991 herein incorporated by reference.

Attached hereto are Exhibits B-F which teach other sex-specific regulatory elements which were known in the art as of the filing date of the instant application and which can be used in practicing the claimed invention without undue experimentation. Exhibit B (Rina and Savakis, (1991) Genetics, 127:769-780) teaches the cloning, characterization and partial sequence of the female-specific VG1 and VG2 regulatory elements in the Medfly *Ceratitis capitata*. Exhibit C (Romans et al., (1995) Insect Biochem. Molec. Biol, 25;939-958) teaches the *Aedes aegypti* female-specific vitellogenin A1 regulatory elements. Exhibit D (Kuhn et al., (2000) Genome, 43;1011-1020) teaches the various conserved structures of the female-specific splicing regulatory elements in the doublsex gene *of Megaselia scalaris*. Similarly Exhibit E (Hertel et al., (1996) RNA, 2;969-981) teaches the female-specific splicing regulatory elements in the doublsex gene of *D. melanogaster*.

Exhibit F (Komitopoulou et al., (2004) Insect Biochemistry and Molecular Biology 34;149-157) is a review summarizing structural and functional studies on Medfly promoters and regulatory elements that can be used for driving sex-specific gene expression. Although this is a post-filing publication many of the Medfly promoters and regularity elements described in the publication, were known prior to the present application's filing date. For example, the

publication describes various male specific regulatory elements, including those for male-specific serum proteins (MSSPs). The publication states on page 150:

> "The MSSP-alpha 2 and MSSP-beta2 genes have identical 5' untranslated regions (5'UTR) and exhibit 94.5% identity along their 504 bp upstream promoter regions, presenting a few nucleotide substitutions and single or small nucleotide deletions (Christophides et al., 2000b)." citing Christophides et al., (2000), Genetics 156;173-182.

The Komitopoulou et al. publication also teaches various female specific regulatory elements including the female-specific chroion proteins. The publication states on pages 152-153:

> The main regulatory elements that are responsible for sex and tissue-specific expression of these genes have been characterized in Drosophila (Swimmer et al., 1990, 1992; Mariani et al., 1996). Six major chorion genes have been isolated from Medfly (Konosolake et al., 1990; Tolias et al, 1990; Valchou et al., 1997) . . . . . Functional studies on the promoter of the med-fly s36 gene in Drosophila transformants HELD that it operates in a similar manner to the Drosophila homologue (Tolias et al., 1993).

In view of the above, the instant application provides sufficient guidance to enable one of ordinary skill in the art to practice the invention with any of the sex-specific regulatory elements which are known in the art.

7 As discussed in detail in the Amendment and Response filed concurrently herewith, the teachings of the above referenced application, in view of what is known in the art, fully enables one of ordinary skill in the art to perform the method of controlling an insect population as recited in claims 1-14 and 21. Particularly, the application teaches success with other insect populations besides *Drosophila*. The publication states on page 18:

> 15 Medfly transgenic lines have been generated using the same transposon. FIG. 2 shows female-specific expression of GFP driven by the *Drosophila* YP promoter in one of these Medfly lines.
>
> Sex-specific expression of GFP protein in some of these transgenic lines has also been documented by Western blot analysis using a commercially available monoclonal anti-GFP antibody (FIG. 4).

It is my belief that in view of the teachings present in the specification, and what was known in the art as of the filing date of the instant application regarding the introduction of insects into a wild-type population, sex-specific regulatory elements, and the transformation of insects, the specification provides more than ample guidance to enable one of skill in the art to perform the method of insect control as claimed in claims 1-14 and 21.

I hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

R.K. Craig 12th November 2004

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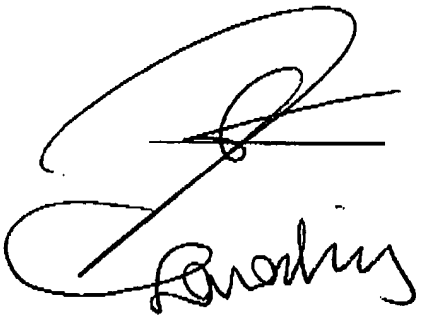

C. SARAKIS

Date

Nov. 12, 04